Making dementia a priority:
changing perceptions, practice and policy.

Alzheimer Europe position on risk disclosure

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1. Background

Extensive research has been conducted since the discovery of Alzheimer's disease (AD) in 1906. However, the multifactorial origin and complex prognosis of the disease have led to disappointing results in the development of pharmacological treatments for AD and to limited effectiveness of current symptomatic therapies.

In this context, and with the growing interest in modifiable risk factors for dementia, AD research has widened the focus to individuals diagnosed earlier in the disease course, i.e. with MCI due to AD[1], and to people at risk of developing cognitive impairment. These groups of people could be potentially included in clinical trials to test new AD treatments, and would hopefully benefit most from future approved drugs to prevent the disease onset and progression.

With the aim of identifying individuals at risk of developing cognitive impairment and people with MCI due to AD, more and more researchers are working on the development of tools and the discovery of new biomarkers which will help predict the risk of cognitive impairment and diagnose AD earlier (i.e. in the MCI stage). If the development of these tools and the discovery and validation of new AD biomarkers were successful enough, they could start being used in clinical studies and clinical settings to predict risk status or to diagnose the disease earlier. Although this kind of research is happening, it is not yet clear how the disclosure process should be for individuals at risk of cognitive impairment and those with MCI due to AD who are at risk of developing AD dementia[2].

In the context of early diagnosis and risk prediction, genetic and non-genetic biomarkers, and lifestyle and environmental factors have become very relevant in the field of AD. The well-known hallmarks of AD, amyloid peptides and tau proteins, are clinically validated and accepted non-genetic biomarkers of this disease. Despite being accurately measured by positron emission tomography (PET) scan and quantified within the cerebrospinal fluid (CSF), PET scans and CSF biomarkers for AD are expensive, invasive, and, sometimes, only offered in specialised medical centres of specific geographic regions. To address this issue, blood-based biomarkers have emerged as a cost-effective and easily accessible alternative for clinical use (Zetterberg and Burnham, 2019). However, their accuracy and validity remain to be proven in large, heterogeneous and multicentric cohorts.

Besides amyloid and tau, mutations (i.e. changes/variants) in apolipoprotein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes are associated with the development of young-onset familial AD (a type of AD that is hereditary and whose symptoms appear at an early age i.e. before the age of 65). These mutations are inherited in an autosomal dominant fashion and have almost complete penetrance. This means that a single copy of a mutated gene from one parent is sufficient to cause the disorder, and that people carrying an altered version of any of these genes are almost certain (i.e. are at absolute risk) to eventually develop the signs and symptoms of AD (Dubois et al., 2021).

In addition to these three genetic variants, the apolipoprotein (*APOE*) gene is believed to have a role in the development of sporadic AD (the type of AD that does not have a specific family link). The most known variants of *APOE* are *APOE Ɛ*2, *APOE Ɛ*3 and *APOE Ɛ*4. Whereas the *APOE* versions *Ɛ*2 and *Ɛ*3 have a protective and neutral effect on the disease, respectively, *APOE Ɛ*4 is associated with an earlier age of cognitive impairment onset and is known to increase the risk of developing AD by 3.7 and up to 12 times relative to the variant *APOE Ɛ*3 (Serrano-Pozo et al., 2021).

[1] MCI due to AD: the predementia stage of AD in which cognitive symptoms are not severe enough to significantly affect everyday activities.

[2] AD dementia: the stage of AD in which the cognitive symptoms are severe enough to affect daily life activities.

Some biological characteristics of an individual's health and lifestyle (e.g. diet, physical activity, level of cognitive engagement, education, hypertension, hearing impairment, smoking, diabetes, alcohol consumption, traumatic brain injury and depression) and the surrounding natural environment (e.g. pollution) may also increase or decrease the risk of cognitive impairment (Livingston et al., 2017, 2020). These modifiable risk factors are reported to account for about 40% of dementias, and it is thought that targeting them might protect someone from developing cognitive decline by reducing brain damage (e.g. amyloid and tau accumulation) and increasing or maintaining cognitive reserve (i.e. brain's ability to find alternative ways to perform a task) (Livingston et al., 2020). However, how long someone at risk of developing cognitive impairment should be exposed to a healthy lifestyle/environment in order to reduce the risk of cognitive impairment and prevent the future development of AD is still unclear (Livingston et al., 2020).

Although they are sometimes used in combination to predict risk, the meaning and implications of the risk that *APOE Ɛ*4, amyloid, tau, mutations in *APP*, *PSEN*1, *PSEN2*, lifestyle and environmental factors represent are different. *APOE Ɛ*4 and mutations in *APP*, *PSEN1* and *PSEN2* represent the unchangeable predisposition that someone has to develop AD, also known as susceptibility. On their behalf, lifestyle and environmental factors contribute marginally to the overall risk of developing cognitive impairment, whereas amyloid and tau build-up, as the potential beginning of AD, significantly increase the risk of developing cognitive impairment (Ossenkoppele et al., 2022). However, unlike the genetic biomarkers *APOE Ɛ*4 and *APP*, *PSEN1* and *PSEN2* mutations, the accumulation of amyloid peptides and tau proteins, and someone's lifestyle and surrounding environment change over the course of life and disease, and may not be sufficient to cause the disease on their own.

A degree of uncertainty is implicit in both terms "MCI due to AD" and "risk of cognitive impairment". People diagnosed with MCI due to AD present a degree of cognitive impairment that can be objectively measured and is not normal for someone or their age, however, they are still largely autonomous in their daily activities (Albert et al., 2011). Although this group of individuals is more likely to progress to AD dementia (Doraiswamy et al., 2014; Vos et al., 2015), the rate of progression from the MCI stage to the dementia stage of AD is not fully understood and may well be very individualised.

Unlike those with MCI due to AD, individuals with amyloid and/or tau aggregation in their brains, and without signs or symptoms of AD should be described as people asymptomatic/at risk of developing AD dementia rather than being classified in the preclinical stage of AD (Dubois et al., 2021; Gove et al., 2016). As well as the progression from MCI due to AD to AD dementia, the evolution of the risk of developing cognitive impairment (caused by amyloid and tau aggregation, lifestyle and environmental factors, and *APOE Ɛ*4) over time is also uncertain. This is due to the inability of risk predictions to determine the clinical trajectory and distinguish cognitively healthy people who will develop cognitive impairment from those who will not (i.e. risk predictions lack clinical validity). In addition, the current lack of specific treatments to prevent the development of future possible cognitive impairment, or to stop the progression from MCI due to AD to AD dementia, currently limits the usefulness of both risk status from the individual and clinical perspectives (Bunnik et al., 2022).

Uncertainty is present in both people considered at risk of developing cognitive impairment and people who actually have a diagnosis of MCI due to AD and are at risk of progressing to AD dementia. However, the disclosure of a risk status for the development of cognitive impairment in people who do not have any previous thoughts about risk (i.e. no family history of AD) or for AD dementia in people with an AD diagnosis is different. The former may be the extent to which AD is likely to happen, whereas the latter means already having the disease and being more likely to progress to AD dementia. In addition, the disclosure of risk status to someone who is cognitively healthy is also affected by personal factors (e.g. age, working age etc.), the personal understanding and how that person makes sense of the risk, and the perceived benefit of available treatments/strategies to reduce risk, prolong someone's independence and cognitive capabilities. These may determine the motivation or reluctance to be assessed for the risk and

to know (or not) the result, and the perception and impact of such risk, if disclosed, on that person's life (Milne et al., 2018). In both cases, however, disclosure of risk should be understood as a gradual conversation (Abe et al., 2019), taking place during multiple appointments, between the clinician/researcher and the person being assessed for the risk, AD biomarkers or cognitive abilities. Regardless of the setting (interventional trials, observational studies, or clinical settings) (Bunnik et al., 2022), the disclosure of a risk prediction for AD or a risk prediction for AD dementia should be always accompanied by pre-counselling.

Alzheimer Europe is involved in several projects that focus on the topic of risk disclosure. This topic has been widely discussed during consultations with several groups of people (i.e. people with dementia, people with MCI due to AD and cognitively healthy people). Based on the literature presented above and the feedback collected during these consultations, Alzheimer Europe proposes the following recommendations to disclose the risk of developing cognitive impairment or AD dementia in a clinical setting, interventional and observational studies:

2. General recommendations when disclosing risk for cognitive impairment to cognitively healthy people or risk for AD dementia to people with MCI due to AD:

- During the pre-counselling phase, different scenarios should be considered including (a) the person is proactively seeking the risk status and asks the doctor and is sent to a memory clinic, and (b) the person wants to participate in research and, as part of the research, the risk status or the cognitive skills are assessed. In scenario (a), some requirements may need to be met e.g. a reason to be assessed for the risk status. In scenario (b), it should be clarified that the assessment is part of the research and discussed whether the person wants (or not) to be told some or all of the results.
- During the pre-counselling phase, clinicians should recommend that the person is accompanied by someone (e.g. family member, friend etc.) when the risk prediction will be disclosed if that person so wishes.
- Clinicians should explain in lay terms the type of tool/test that will be used to determine the level of risk for cognitive impairment or for AD dementia, what the tool/test can do and also its limitations. If possible, the person should be given a leaflet with all the information about the tool/test in lay terms that he/she can take home.
- Clinicians should acknowledge that person's concerns and fears (if any) about that tool/test (lumbar puncture, artificial intelligence-based tools etc.) and the possible findings while providing the right amount of information, and adapting it to that person's needs to ensure a clear understanding.
- Clinicians should be transparent about the current therapies and interventions, their capacity for beneficial change and limitations. When recommending the adoption of healthy lifestyle choices, clinicians should clarify that the healthiest of lifestyles cannot, unfortunately, guarantee that someone will not experience cognitive impairment or AD dementia.
- Clinicians should also be transparent about the uncertainty of the clinical progression toward cognitive impairment or AD dementia. A risk prediction for cognitive impairment or AD dementia will never bring certainty or information about the likely course of the risk or the disease progression.
- Clinicians with expertise in neurodegenerative diseases leading to dementia should be the ones responsible for disclosing the risk status for future cognitive impairment or for AD dementia. To do so, clinicians should be allowed to allocate enough time and, if needed, be supported to develop the skills to communicate, explain, and give the person time to understand such risk predictions.
- The level of risk is often referred to as high, low, positive, negative, elevated and non-elevated. In some projects where Alzheimer Europe was part of, cognitively healthy

people, people with MCI, and people with dementia expressed a range of different preferences on this issue, such as high, low, traffic light symbolism, images of people shaded in to represent proportion having it, percentages, ranges etc. In view of the different opinions, we suggest combining numerical terms and the visual context, and providing clinicians with the tools to be able to adapt how they present the results to patients and research participants depending on their needs, preferences and ability to understand.

- Clinicians, researchers or counsellors should guide and inform the person on how to act on the results received (e.g. changes in lifestyle that could be made, support groups to join for psychological and emotional counselling, clinical trials from which that person might benefit etc.). Regular appointments should be offered to both monitor the person's clinical progression and support the person.

3. Specific recommendations when disclosing risk for cognitive impairment to cognitively healthy people:

- Clinicians should inform the person about the type of risk (i.e. modifiable vs. non-modifiable) that the test or tool will measure as this may help understand the implications of the result. For example, in the absence of cognitive impairment, the risk of someone with amyloid accumulation in the brain is not the same as that of someone who carries mutations in *APP* and *PSEN1*.
- Clinicians should inform the person about the possible psychological consequences (e.g. harm and distress) of receiving a risk prediction for cognitive impairment.
- Clinicians should also consider and acknowledge the personal utility that a risk prediction for cognitive impairment may have for the individual. Some people may want to use this information to participate in a dementia prevention clinical trial, and/or to prepare themselves and their families for a possible future with AD.
- Clinicians should also consider and acknowledge personal factors, such as age, working age, personal view about available drugs to prevent the development of AD etc. These factors may contribute to the impact that a risk prediction will have on someone's personal and working life and how that person is going to approach life (e.g. accelerate travel plans, take on new challenges, or devote more voluntary time to charity work etc.)
- Clinicians must always identify the person's wishes and respect the right and wish (not) to know. This should be justified with full consent (Hughes et al., 2017; Vanderschaeghe et al., 2018) to make the disclosure of the risk status for cognitive impairment as timely as possible for each person's situation and wishes.
- Clinicians should ensure that the person still wants to receive the results of the test before disclosing the predicted risk.
- If different factors, such as time constraints, make it unrealistic for clinicians to manage the disclosure process, then other professionals (e.g. counsellors etc.) should be involved in this process.
- Clinicians should make sure that the results are not misunderstood or misperceived. It is important that people understand the difference between absolute risk (i.e. carriers of autosomal dominant mutations (*APP*, *PSEN1*, *PSEN2*)) and relative risk (e.g. amyloid or tau accumulation etc.), modifiable and non-modifiable risk and what is being communicated to them.
- Clinicians and researchers must always refer to cognitively healthy people at risk of developing cognitive impairment as people at risk of developing AD dementia instead of people in the pre-clinical stage of AD (Gove et al., 2016).

4. Specific recommendations when disclosing the risk for AD dementia to people with a diagnosis of MCI due to AD:

- Clinicians should inform the person about the possible psychological and social consequences (e.g. harm, distress, stigma, discrimination from family, friends and/or co-workers and other forms of discrimination, such as in driving, voting and employment (Clark et al., 2022; de Wilde et al., 2018; Hughes et al., 2017)) of having a diagnosis of MCI due to AD and receiving a risk prediction for AD dementia. Information about the kind of measures that will be taken to protect someone's results (e.g. from insurance companies, employment discrimination, commercial companies etc.) and someone's rights at work must also be provided (Gove et al., 2016).

Regardless of whether researchers or clinicians are disclosing risk status for cognitive impairment or for AD dementia, and how AD is addressed in the future, clinicians and researchers should always take the time needed for the whole process (i.e. for pre-counselling and disclosure), while communicating in a careful, confident and honest way (Alpinar-Sencan and Schicktanz, 2020; Frederiksen et al., 2020; Milne et al., 2018).

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